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(R)-13-HYDROXY-CIS-9,TRANS-11-OCTADECADIENOIC ACID, THE PRINCIPAL FATTY ACID FROM CORIARIA NEPALENSIS WALL. SEED OIL

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According to a recently postulated scheme, the title compound is biochemically related to the *cis*-9,*trans*-11,*trans*-13-conjugated triene system that occurs frequently in fatty acids from plants (2). Moreover, Dolev, Rohwedder, and Dutton have just shown that incubation of linoleic acid with a plant lipoxidase leads exclusively to formation of a 13-oxygenated 9,11-octadecadienoic acid (3). While we were preparing this paper, the conversion of linoleic acid to 9-hydroxy-10,12- and 13-hydroxy-9,11-octadecadienoic acids by a prostaglandin-synthesizing animal enzyme system was reported (4). Previous reports have presented evidence for the occurrence in seed oils from seven species of a 13-hydroxy-9,11-octadecadienoic acid. However, it was always present in relatively small amounts and was obtained as approximately 1:1 mixtures with the isomeric 9-hydroxy-10,12-octadecadienoic acid (5,6). The complete stereochemistry of neither component of such mixtures has been published.

We describe here the isolation as the methyl ester and characterization of a 13-hydroxy-9,11-octadecadienoic acid which occurs as the major fatty acid in a seed oil, is optically active, and is not accompanied by detectable amounts of the isomeric 9-hydroxy-10,12-octadecadienoic acid. This 13-

hydroxy-9,11-octadecadienoic acid, for which we propose the name coriolic acid (7), has one *cis* and one *trans* double bond, and we have shown that the *trans* double bond is adjacent to the hydroxyl-bearing carbon atom, as predicted on biochemical and mechanistic grounds (2,6). Thus, the complete structure of coriolic acid is

$$CH_3(CH_2)_4\overset{\underline{R}}{C}HOH\overset{\underline{t}}{C}H{=}CH{-}\overset{\underline{c}}{C}H{=}CH{-}(CH_2)_7COOH.$$

Mixed methyl esters were prepared by treatment of *Coriaria nepalensis* Wall. (family Coriariaceae) seed oil with sodium methoxide in methanol (8). Methyl coriolate, 1.59 g., λ_{max}^{neat} 2.92 (OH) 10.15 and 10.50 (*cis-trans* conjugated diene, see reference 9), $\lambda_{max}^{CH_3OH}$ 233 (ε 27,063), $[\alpha]_D^{23}$ -7.5° (*c* 2.3 in hexane), was isolated as the sole hydroxy ester from 2.42 g. of the mixed methyl esters by countercurrent distribution with an acetonitrile-hexane (1:1) solvent system. A single spot was obtained when methyl coriolate was examined by thin-layer chromatography (TLC). A known mixture of methyl 13-hydroxy-9,11- and 9-hydroxy-10,12-octadecadienoates was chromatographed simultaneously and gave two spots as reported (6). Each of the reference compounds had one *cis* and one *trans* double bond, and as expected, one of the reference spots had the same R_f as methyl coriolate.

The double bonds and hydroxyl group in methyl coriolate were located by oxidative cleavage with a mixture of potassium permanganate and sodium periodate (10). The products were hexanoic acid, determined as such by gas-liquid chromatography (GLC) (11), and nonanedioic acid, which was esterified with diazomethane (12) before identification by GLC. These products established coriolic acid as either 13-hydroxy-9,11-octadecadienoic acid (I) or 9-hydroxy-10,12-octadecadienoic acid (II). To distinguish between the two alternatives, the methyl hydroxystearate, m.p. 56-57° (13), Found: C, 73.0, H, 12.4, obtained from methyl coriolate by catalytic hydrogenation was oxidized with chromic acid in acetic acid.

Since the main products (III-VI) were those expected from methyl 13-hydroxystearate, the structure of coriolic acid is established as I. .

$CH_3(CH_2)_4CHOHCH{=}CH{-}CH{=}CH(CH_2)_7COOH$ (I)

$CH_3(CH_2)_4CH{=}CH{-}CH{=}CH{-}CHOH(CH_2)_7COOH$ (II)

$CH_3(CH_2)_3COOH$ (III)

$CH_3(CH_2)_4COOH$ (IV)

$HOOC(CH_2)_{10}COOCH_3$ (V)

$HOOC(CH_2)_{11}COOCH_3$ (VI)

Products III and IV were determined as such by GLC; the half esters were first converted to diesters by treatment with diazomethane. Small quantities of shorter chain homologs of V and VI were found, but no trace of nonanoic or decanoic acid was detected. Nonanoic and decanoic acids would have been formed from any of the isomeric methyl 9-hydroxy-10,12-octadecadienoate that might have been present in the methyl coriolate sample.

The position of the hydroxyl group in coriolic acid was confirmed by mass spectrometry of the hydrogenation product. The observed prominent ions with mass-to-charge ratios of 211, 214, and 243 were as predicted for methyl 13-hydroxystearate by the fragmentation pattern established for hydroxy fatty esters by Ryhage and Stenhagen (14).

Methyl 13-hydroxystearate and methyl 12-hydroxystearate exhibit plain negative ORD curves, virtually superimposable ($[\alpha]^{23}_{350}$ -0.93 and -1.04, respectively, *c* 2.5 in methanol); this indicates that they have the same absolute configuration. Since the 12-hydroxy isomer is of known (15) configuration, which can be designated *R* according to the sequence rule (16), we conclude that the 13-hydroxy ester and, in turn, the parent coriolic acid also have the *R* configuration.

Figure 1 shows the pertinent regions of the 100 Mcps. PMR spectrum of methyl coriolate. Also shown is the complete first-order analysis of the conjugated olefinic multiplets determined on the basis of the spin decoupling study employed to determine the geometry of the double bonds. Strong irradiation of the carbinol proton $H_{(13)}$ at 405 cps. decoupled it from $H_{(12)}$, centered at 556 cps., and caused the $H_{(12)}$ doublet-split-doublet to collapse to a simple doublet with a splitting of 14.4 ± 0.6 cps., which is typical of a *trans* proton coupling across a double bond. Thus, the double bond adjacent to the hydroxyl carbon must be *trans*. Irradiation of the allylic methylene protons $H_{(8)}$ at 214 cps. decoupled $H_{(9)}$ and caused the triplet-split-doublet centered at 530 cps. to collapse to an 11 ± 0 cps. doublet, a value typical of *cis* double-bond couplings. Therefore, the second double bond is *cis*.

In support of these conclusions, a similar study was carried out with methyl dimorphecolate, which has a 9-hydroxy-*trans*-10,*trans*-12-octadecadienoic structure (17), as a model compound. As expected, the coupling across the double bond adjacent to the hydroxyl carbon is 14.5 ± 0.5 cps. and the coupling across the second double bond is 14.0 ± 0.6 cps.

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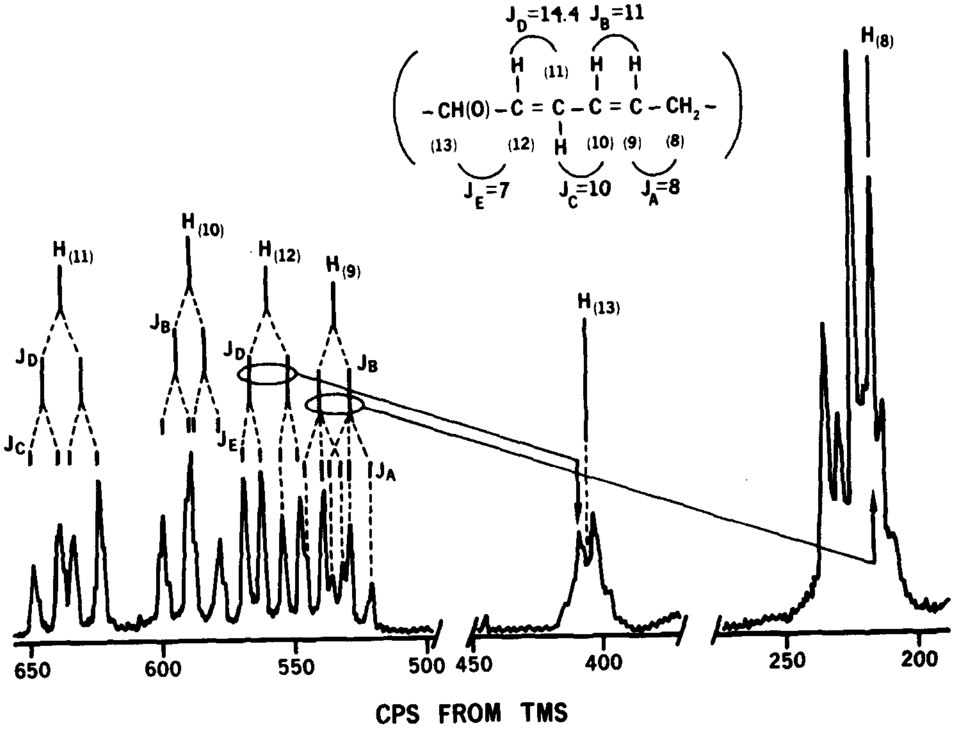

FIG. 1. Portions of 100 Mcps. PMR spectrum of methyl coriolate in CCl_4 and first-order analysis of olefinic multiplets.

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